Sexual Dimorphism in the Expression of Pain Phenotype in Preclinical Models of Rheumatoid Arthritis

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KEYWORDS

• Rheumatoid arthritis • Pain • Sexual dimorphism

KEY POINTS

- Rheumatoid arthritis is the most frequent rheumatic disease with a higher prevalence in females than in males.
- Pain is a cardinal symptom of rheumatoid arthritis and strongly impacts patient quality of life.
- Sexual dimorphism in pain processing has been described in the literature since 1988.
- Sexual dimorphism in rheumatoid arthritis has been reported. However, there remains a dearth of studies directly addressing sexual dimorphism in rheumatoid arthritis pain mechanisms.

A BRIEF OVERVIEW OF RHEUMATOID ARTHRITIS

Historically, rheumatoid arthritis (RA) was first described in 1800.[1] It is at present the most frequent chronic inflammatory rheumatic disease.[2] RA prevalence ranges from 0.3% to 1.0% of the population in industrialized countries according to the World Health Organization[3,4] and its incidence increases with the aging of the population.[5,6] This disease is characterized as an autoimmune-mediated inflammatory disease that involves both immunologic activation and inflammatory pathways. Once these pathways are triggered, it results in a self-perpetuating process that leads to joint inflammation, cartilage degradation, bone erosion, and chronic pain.[7] Identification and prognosis of patients with RA have been improved with the recognition of specific anticitrullinated peptide antibodies (ACPA)[8] in addition to rheumatoid factor.[9] Indeed, the detection of anticyclic citrullinated peptides antibodies (anti-CCP) presents with a

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98% specificity and are thus considered as useful tools for the diagnosis of rheumatoid disease.[10] Although the dynamic process of rheumatic disease initiation and progression is not clear, a robust association between genetic,[11–15] epigenetic,[16–21] environmental,[22–29] and immunologic[30–34] components during the development of RA has been demonstrated.

From the genetic perspective, it is well-recognized that RA susceptibility may be strongly linked to family history.[35] The increased prevalence of disease within racial groups has been shown, as in native Americans where prevalence rates of RA of 5% to 7% have been reported.[36] Since the early 1970s, class II human leukocyte antigens (HLA) were associated with susceptibility to RA.[37,38] The major HLA susceptible locus associated with RA is *HLA-DRB1*, especially with regard to a specific sequence of amino acids referred to as "the shared epitope" in different *HLA-DRB1* alleles (eg, **01, *04, *10, *14*).[39] Specific amino acids at position 11 (eg, Val, Leu, Pro) or 13 (eg, His and Phe) are strongly associated with RA development.[40,41] Other non-HLA genes have been shown to be associated risk factors for developing RA, including *PTPN22, TNF, IL-1B, CRP,* and *CTL4*.[13–15,42] Although these genetic associations with RA susceptibility are robust, there is not a perfect genetic consonance and other factors clearly can contribute to the development of RA. Associated variables that have been strongly implicated in the development of RA include environmental factors, such as cigarette smoking,[22] pollutants (eg, silica),[43] and patient variables (eg, diet),[44] mucosal microbiomes,[28,29,45–47] and sex/gender.[48,49]

Of particular interest in this review is the issue of the sex linkages and the development and progression of RA. The RA diagnosis in fact presents as a heterogeneous phenotype, the severity and patterns of which are influenced by sex-associated factors. RA is 2 to 5 times more common in women than men, depending on the region in the world.[5,6] In women, RA onset is commonly seen between 30 to 60 years of age, whereas in men, RA often begins later in life.[50] Thus, after the age of 65, the ratio of the incidence in men and women shifts with the predominance occurring in men more than 75 years of age.[49] Although it is not clear which factors drive the sexual dimorphism in patients with RA, comparing clinical data in humans, and preclinical studies in rodents, several hypotheses have been proposed based on sex hormones[51–53] and immune cells.[54]

PAIN IN RHEUMATOID ARTHRITIS

Model of Phases of Pain in Rheumatoid Arthritis

The mechanisms underlying pain state in the patient with RA represent complex processes that differ between stages of the disease (**Fig. 1**).[55] The production of autoantibodies (eg, rheumatoid factor, ACPA, anti-CarP) starts months to years before the onset of the disease, gradually increasing[56] (dark blue line; see **Fig. 1**, ❶). We now recognize in the early preclinical arthritis phase, patients can suffer from arthralgia (purple line; see **Fig. 1**, ❶) before the development of clinically evident signs, such as palpable synovitis (dotted blue line; see **Fig. 1**, ❶). In the subsequent development of active disease (eg, with clinical signs of joint pathology), patients with RA develop chronic inflammatory joint pain, which display a cyclic waxing and waning (see **Fig. 1**, ❷). These clinical signs may then display some degree of remission after treatment with modern therapies. In remission, pain resolves in some patients (see **Fig. 1**, ❸), but in a significant proportion of patients arthralgia persists[57] (see **Fig. 1**, ❹). Moreover, remission is not necessarily associated with declining autoantibody titers and disappearance of autoantibodies remains rare[58] (dotted dark blue line; see **Fig. 1**, ❹). Mechanisms involved in RA pain are also different between stages (for an extensive literature on this subject see reviews[55,59–62]).

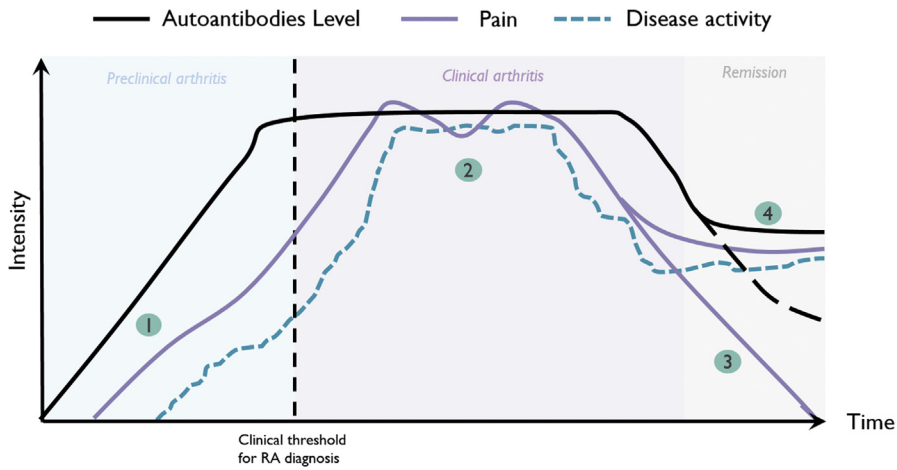

Fig. 1. Pain evolution according to RA disease activity. In RA, pain symptom in patients follows different steps[55]: ❶ in a preclinical stage, patient can develop arthralgia before the onset of the disease potentially associated with an early production of autoantibodies, ❷ after RA diagnostic, in clinical stage, marked by the development of synovitis, pain and disease activity both increase and fluctuate without being entirely correlated each other, ❸ following an effective therapy, pain symptom can decrease in a remission stage, but ❹ in a significant proportion of patients, pain symptoms persist even though the disease activity decreased.

Simplistically, pain processing begins with the activation of nociceptive primary afferents, which innervate the joint.[63] In turn, these nociceptive afferents lead to the activation of second-order neurons in the spinal dorsal horn that project via the ventrolateral long tract to a variety of supraspinal centers in the brain. Some of these projections through the somatosensory thalamus to the somatosensory cortex mediate the so-called sensory discriminative aspect of pain, whereas other projections are through more medial thalamus regions and project to the areas of the limbic forebrain associated with emotion and affect. The consequence is the pain state, which comprises the emotional and affective factors that lead, ultimately, to a protective response.[63,64] Although the acute activation of these circuits normally have a protective role (eg, to evoke for example limb withdrawal), these states, when chronic, become maladaptive. Such chronic pain attributes in RA have a marked prevalence in females.[65–67] However, there is no common pathophysiologic sex-related mechanism shared by all chronic pain conditions; each one can present specific factors that differ between females and males.[68]

Lack of Covariance with Physical Signs and Pain in Rheumatoid Arthritis

An important point to be made in the conceptual summary displayed in **Fig. 1** is that, although joint morphology, pathology, and loss of function primarily underlie the RA diagnosis, pain displays deviations from the expression of the underlying clinically evident pathology for the patient with RA. Of note, this dissociation has particular relevance in that pain is the cardinal symptom of RA that strongly impacts these patients' quality of life.[69] In fact, 75% to 80% of patients with RA in treatment have moderate to severe pain symptoms.[70,71] Only 26% of patients are satisfied with their RA treatment[69] and between 55% and 65% of patients are unsatisfied with their pain management,[70] a priority for patients with RA.[71] It is important to take into account that most of

data are obtained from women (75%–90% depending on the study[69,70]). The actual "treat to target" strategy for RA aims to decrease the pathologic changes[72] and thereby to modulate pain. However, joint pain is in fact poorly correlated with the inflammatory state of the patient with RA.[62] Even with optimal regulation of inflammatory cascades, pain has often been shown to be insufficiently controlled.[57] It is well-appreciated that joint pain (arthralgia) often begins before other manifestations of joint inflammation[73,74] and consequently before any diagnosis or the implementation of an RA therapeutic strategy. A further complexity is that, although the RA phenotype involves joint structures (synovia, cartilage, and bones), an autoimmune response outside of the joint is also observed and is usually associated with other pathologies, such as rheumatoid nodules, lymphatic vessel tumefaction, pleuritis, and cardiovascular or ocular manifestations.[75] These observations have led to an appreciation that pain arising in association with RA may reflect parallel processes that may be influenced by the variables that are associated with the physical manifestation of RA and particularly given the role played by sex.

Covariance of Antibodies with Pain and Dissociation from Joint Manifestations

As presented in conceptual summary in **Fig. 1**, arthralgia can in fact be reported months to years before the actual onset of clinically identified disease. It is now appreciated that this onset of arthralgia may occur concurrently with the expression of autoantibodies (ie, rheumatoid factor,[76] ACPA,[77–79] anti-CarP,[80–82] and anti-MAA[83,84]). These autoantibodies can be detectable in patients reporting predisease arthralgias and may be associated with persistent arthralgia during remission. Recently, a direct link between ACPA isolated from patients with RA and pain development in mice has been described[85] and was felt to mechanistically involve chemokine production by osteoclasts.[86] Phenotypic changes of in the Fc portion of antibodies, such as galactosylation, fucosylation, or sialylation, could be involved in the proinflammatory profile acquisition and certainly pronociceptive.[87–90] In addition to autoantibodies, RA is marked by an early alteration of cytokines and chemokines levels, such as IL-5 or IL-17A,[90–93] which are directly able to sensitize the nociceptor.[63]

As indicated in **Fig. 1**, during the clinical stage, synovitis development induces a chronic joint pain marked by peripheral and central sensitization initially induced by immune cells in RA.[55] It is interesting to note that a comorbid condition, fibromyalgia, reflects a chronic widespread pain associated with tenderness, sleep disturbance, and psychiatric distress in the absence of clinical signs of inflammation. This condition affects around 14% to 20% of patients with RA, with a higher prevalence in women.[94,95]

PRECLINICAL MODELS AND SEXUAL DIMORPHISM IN THE PAIN PHENOTYPE OF RHEUMATOID ARTHRITIS

Given the complexities of pain in different stages of arthritis, research efforts have focused on drawing parallels between sex differences observed in RA pathophysiology and sex differences underlying the pain phenotype observed clinically and in preclinical models of RA.

Use of Rodent Models in Arthritis Studies to Study the Role of Sex

Pioneering studies on the sexual dimorphism of pain expression began to emerge around 1988, when Bodnar and associates[96,97] demonstrated sex differences in basal nociceptive thresholds in rodents that seemed to be modulated by sex hormones. In particular, a large number of publications came in the mid-1990s and drew

considerable attention to the topic.[66,68,98] Previously, most preclinical studies traditionally used males as subjects and the sex-related differences in pain and their mechanisms were not explored widely. In 2016, the National Institutes of Health initiated a policy requiring preclinical research to use males and females in supported research. Currently, it is clear that males and females do not manifest the same pain experience, showing different physiologic and behaviorally defined pain responses.[67–74] As reviewed elsewhere in this article, overall, females, in preclinical models, often present a lower threshold and or a heightened pain response than that observed in males.[99–101]

Preclinical animal models of RA have been used to understand the pain phenotype and response to analgesic drugs during development and maintenance of RA and can be used to concurrently examine male and female rodents. Here we introduce animal models of RA that have been used to understand sexual dimorphism in the RA pain phenotype and studies directly addressing different hypotheses in relation to pain mechanisms at the levels of primary afferent neurons, dorsal root ganglia (DRG) and trigeminal ganglia, the dorsal horn of the spinal cord, and supraspinal structures.

Several preclinical models have been widely used to understand pain processing and sexual dimorphism in RA (for review see[61,102,103]). Broadly speaking, these models represent the induction of monoarthritis or polyarthritis with time-dependent changes in the joint morphology (eg, synovial lesions, bone resorption, and cartilage destruction), in the inflammatory phenotype (eg, synovial inflammation, infiltration of immune cells), and in the development of pronounced and ongoing pain and changes in behavior, including pain evoked behaviors (eg, mechanical and thermal thresholds), pain-suppressed behaviors (eg, feeding, mating, and locomotor activity), and operant conditioning (eg, conditioned place preference).[102] As will be noted, in comparison with the immunization model, collagen-induced arthritis, the collagen-antibody–induced arthritis (CAIA), and K/BxN models present over time evidence of evolving pain phenotypes.[104] A brief description of these models is presented.

i. The complete Freud's adjuvant (CFA) generated by an intradermal injection[105] (polyarthritis) or an intra-articular injection of CFA (monoarthritis).[106,107] This model is mediated by the innate immune system and leads to the infiltration of inflammatory cells, synovial hypertrophy, and joint alterations, as well as inflammatory response in the viscera, skin, and muscle. These rodents develop hypersensitivity to innocuous stimuli with an immediate onset (<24 hours) and persisting for weeks.
ii. The collagen-induced arthritis model, which is induced by intradermal injection(s) of type II collagen that activate the adaptive immune system and the production of anticollagen II antibodies. This model of polyarthritis leads to a breach of self-tolerance, T- and B-cell activity and activation of anticartilage immunity.[108] In this model, animals develop hypersensitivity at the onset of the disease (within the second week) that persists for at least 28 days.
iii. The CAIA model is induced by an intraperitoneal or intravenous injection of a cocktail of anticollagen II antibodies followed by an intraperitoneal injection of lipopolysaccharide to synchronize the onset of inflammation. The CAIA model of polyarthritis does not involve T and B cells, but directly uses antibodies against joint-specific epitopes, leading to synovial inflammation, the infiltration of immune cells, and the destruction of bone and cartilage. In this model, mechanical hypersensitivity precedes the inflammatory phase and persists for 3 to 4 months, even after the resolution of inflammation.[61]
iv. The K/BxN passive serum transfer model of polyarthritis is induced by the intraperitoneal injection(s) of sera from KRN-NOD (K/BxN) transgenic mice that

demonstrate an inflammatory arthritis phenotype that begins shortly after weaning and continues unabated into adulthood.[109] The serum from the transgenic K/BxN mice contains antibodies directed against glucose-6-phosphate isomerase and associated immune complexes, leading to synovial inflammation, the infiltration of immune cells, and the destruction of bone and cartilage. This model is characterized by a biphasic period where tactile and cold allodynia are observed very early after the delivery of the K/BxN serum.[110] The clinical signs (eg, joint swelling, erythema) resolve and, of note, the allodynia persists unabated. As noted in **Table 1**, the early phase displays an inflammatory analgesic pharmacology, whereas the late phase seems to represent an analgesic pharmacology of a neuropathic state.

As shown in **Table 1**, in the models as described elsewhere in this article, a sexual dimorphism for arthritis score, pain phenotype, neuraxial changes, and response to treatment has been a focus of limited research to date with direct comparisons. Regarding inflammation, females exhibited a higher arthritis score in CFA rats and female rats with collagen-induced arthritis had a greater susceptibility than males, whereas in the CAIA and K/BxN passive transfer models, no difference was observed in arthritis development between sexes (in mice). For the pain phenotype, a sexual dimorphism was observed in female CFA rats that presented a lower evoked paw pressure threshold, whereas there were no differences in the collagen-induced arthritis male and female rats. In contrast, female K/BxN passive serum transfer mice showed a resolution in both paw inflammation and evoked mechanical allodynia pain phenotype in the late phase, whereas males presented a postinflammatory and long-lasting allodynia.

Major sexual dimorphism was observed in the molecular mechanism of pain processing; indeed, in the CAIA and K/BxN models. Female mice showed a spinal microglia (ie, the ionized calcium binding adaptor molecule 1 marker) activation in early and late phases and astrocyte activation (ie, the glial fibrillary acidic protein marker) only in the late phase. Interestingly, K/BxN male mice presented only microglial activation in the late phase and no significant astrocyte activation. In the CAIA model, both males and females showed an increase of spinal calcitonin gene-related peptide and substance P, key neuropeptides involved in central sensitization playing a role in the development and maintenance of hyperalgesia,[114] but spinal galanin, a neuropeptide known to be involved in neuropathic pain, was only increased in males in the late phase of CAIA. In the K/BxN model, both males and females show an enhanced expression of tumor necrosis factor in the spinal cord at the peak of paw inflammation. However, also in the spinal cord females showed enhanced IL-10 messenger RNA (mRNA) and in the late phase increased type I interferon-beta mRNA expression compared with male mice. These protein and mRNA markers are leading to our cellular and molecular understanding of the sex differences seen in the pain phenotypes in arthritis.

In addition to the differences in the biomarkers of pain, there were sex differences in the responses to pharmacologic treatments. In the CFA model, opioid agonists (eg, morphine, butorphanol, oxycodone, and loperamide) were more potent in males than in females. Intrathecal administration of glial inhibitors using minocycline or pentoxifylline were only effective in male CIAI mice, highlighting a prominent role for microglia in male pain processing. Intrathecal injections also demonstrated that pain modulation was largely at the spinal cord/DRG level in the K/BxN model. In the K/BxN mice, intrathecal injection of anti-tumor necrosis factor antibodies transiently reduced pain as did the injections of interferon-ß. Neither single agent was effective

Table 1
Sexual differences in preclinical models of inflammatory arthritis

Model	Species	Arthritis Score	Pain Phenotype	Neuraxial Changes	Response to Treatment	References
CFA	Lewis rats	♀>♂	♀>♂	Not investigated	Morphine 5 times more potent in ♂-treated CFA vs ♀ Butorphanol 62 times more potent in ♂-treated CFA vs ♀ Oxycodone greater % of antihyperalgesia in ♂-treated CFA vs ♀ Loperamide 4 times more potent in ♂-treated CFA vs ♀Naloxone ♀ = ♂	Cook & Nickerson,[105] 2005
CIA	Lewis rats Dark agouti rats Spragues Dawley rats	♀>♂	♀ = ♂	Not investigated	Tropomyosin receptor kinase A inhibitor AR786 reduced pain behavior - data for ♀ and ♂ were not separated	Ashraf et al,[111] 2016; Dimitrijević et al,[54] 2020
CAIA	Balb/c mice CBA mice C57BL/6 mice	♀ = ♂	♀ = ♂	In the spinal dorsal horn: ↗Ibal immunoreactivity early and late phase ♀ = ♂ ↗GFAP late phase ♀ = ♂ ↗Galanin late phase only in ♂	Minocycline and pentoxifylline reversed mechanical hypersensitivity in the late phase only in ♂	Fernandez-Zafra et al,[112] 2019
K/BxN	C57BL/6 mice	♀ = ♂	Early phase ♀ = ♂ Late phase ♀<♂	In the spinal cord: mRNA TNF ♀∼♂ mRNA IL-10 ♀>♂ mRNA interferon–ß ♀>♂ In the spinal dorsal horn: ↗Ibal early and late phase in ♀ but only late phase for ♂ ↗GFAP late phase only in ♀	♂anti-TNF + interferon-ß in the early phase reduced allodynia for at least 7 d	Woller et al,[113] 2019

Abbreviations: ♀, female; ♂, male; CFA, complete Freud adjuvant; CIA, collagen-induced arthritis; CAIA, collagen antibody-induced arthritis; K/BxN, K/BxN serum transfer; GFP, glial fibrillary acidic protein; TNF, tumor necrosis factor.

in the long term; however, 2 injections with both agents permanently reversed the pain phenotype in male mice. This result suggested that the spontaneous biologic advantage of self-remitting pain in female mice could be phenocopied with therapeutic injections of biologic agents at the anatomic level of the difference between male and female pain mechanisms (in this case the intrathecal space).

The Role of Sex Hormones

Sexual dimorphism in the pain experience is probably mostly defined by sex hormones. Although the effect of these hormones on pain is complex and not yet completely understood, it is well-known that sex hormones influence both peripheral and central nervous system pathways by modulating neuronal activity.[115] Considering sex hormones in patients with RA, it is well-known that, during pregnancy, circulating steroid hormones (ie, estrogen, progesterone, and cortisol) seem to directly or indirectly suppress synovial inflammation inhibiting the maternal immune system and inducing an immune tolerance.[51] Moreover, postpartum, breastfeeding is associated with a lower risk of RA[52] and the production of prolactin that has immunomodulatory properties.[116] Furthermore, RA is more frequently observed after menopause and menopause at a young age ($\leq$45 years old) is a risk factor for RA.[53] Some studies also demonstrated a protective effect of progesterone receptor signaling in mice[117] and androgen may also protect against RA development in humans.[118] Conversely, androgen deprivation therapy[119] or hypogonadism[120] increases the risk of RA in men. Therefore, a sexual dimorphism in the expression of pain phenotype in RA is undoubtedly associated, in part, by sex hormones.

Hormonal Receptors on Neurons

Androgen receptors (AR) are expressed in DRG sensory neurons and one-half of AR-positive neurons were nociceptive afferents[121]; some studies have demonstrated the involvement of testosterone in pain modulation.[122–125] It has been shown that primary afferents also express estrogen receptors (ERα and ERβ).[126,127] Preclinical models have shown that ERα expression seems to be restricted to nociceptive afferents whereas ERβ is more widely distributed.[128] It has been demonstrated that ERs can play a role in the control of peripheral nociceptive signaling by interacting with purinergic, P2X3, and transient receptor potential vanilloide 1 receptors in nociceptive afferent neurons.[127,129–133] The expression of both P2X3 and transient receptor potential vanilloide 1 receptors was significantly reduced in female ERs (ERα and ERβ) knockout mice compared with the expression in female wild type mice. Ma and colleagues[130] demonstrated that ovariectomized female rats had an increase of P2X3 expression in DRG neurons followed by a higher mechanical sensitivity, which were reversed by estrogen replacement. In contrast, mechanical sensitivity and P2X3 expression did not change in the DRG of orchiectomized male rats, evidencing the relation between estrogen and P2X3 expression in nociceptive afferents. Because P2X3 receptors are expressed in the fibers innervating joints, this relation between estrogen and P2X3 receptors might explain, at least in part, the sex differences in pain observed in RA.

In addition, estrogen can also mediate the sex-related differences in substance P release[134] and in the expression of both nerve growth factor and its high-affinity receptor tropomyosin receptor kinase A in DRG neurons.[135–137] Substance P expression is altered in the joint and dorsal horn of animals with arthritis.[138,139] Nerve growth factor and its receptor are involved in pain[140] and rheumatic diseases.[141] Calcitonin gene-related peptide expression in DRG neurons also undergoes an estrogen influence.[142] Therefore, the effects of estrogen on nociceptive neurons may also

be contributing to the sexual dimorphism in the pain phenotype of RA. However, studies are needed comparing the female and male pain phenotypes and their nociceptive afferent proteomic profiles. This need is more pronounced when a specific condition is considered. Sensory afferent neurons also express prolactin receptors, which modulate neuronal activity majorly in females.[143] Patil and colleagues[143] have shown that prolactin receptor mRNA was expressed equally in female and male peptidergic nociceptors and central terminals; however, prolactin protein was found only in females, and, in turn, prolactin-induced excitability was detected only in female DRG neurons. Strikingly, in patients with RA, both males and females, increased serum levels of prolactin cooperates with other proinflammatory stimuli to activate macrophages,[144] but the clinical significance of prolactin to RA pathogenesis remains unclear. Taking into account these recent data in the literature, it is plausible that, during RA development, primary afferent neurons could play a role in sexual dimorphism of the RA pain phenotype.

Sex Differences in Transcription at the Dorsal Root Ganglion

The sexual dimorphism in response to a noxious stimulus can involve differences at the level of primary afferent neurons, dorsal root and trigeminal ganglia, dorsal horn of the spinal cord and supraspinal structures. DRG and trigeminal ganglia primary afferent neurons have been found as possible source of mechanistic diversity that causes sex differences in pain.[143,145] In fact, studies suggested sex-related differences in the sensory neuron transcriptome. A transcriptomic analysis of DRG shows that prostaglandin D synthase, an enzyme involved in prostaglandins E2 production is upregulated in female neurons.[143,145] Prostaglandins E2 is well-known to be involved in pain processing by inducing neuronal sensitization. Indeed, cyclo-oxygenase inhibitors have been widely used in pain management. Importantly, studies in rodent arthritis models have described decreased inflammation in cyclo-oxygenase–deficient mice in females, but not in males.[146] However, in the same study, pain and sexual dimorphism were not analyzed.

Sex Differences in Microglia and Macrophages

The sensory afferent neuron forms an excitatory synapse with second-order neurons in the dorsal horn of the dorsal spinal cord to initiate transmission in the central nervous system. A sexual dimorphism in pain processing in the spinal cord has been described in the literature,[67,147] including in animal models of RA (see **Table 1**). Mogil and colleagues have shown that hypersensitivity in inflammatory and neuropathic pain conditions in mice, can be attributed to distinct immune cell types: microglia in males and T cells in females.[148,149] Corroborating this finding, the response to intrathecal administration of glial inhibitors are only effective in males and not in females in CAIA mice[112] (see **Table 1**) and reinforced a sex difference in pain neuraxial mechanisms. The purinergic receptor P2X4 is known to play key roles in inflammatory response[150] and is involved in a sex-dependent manner in various pain conditions.[151] In neuropathic pain, a male-specific upregulation of P2X4R has been shown[148] and an inhibition of spinal P2X4R attenuates pain hypersensitivity in males but not females mice,[152] which raises the questions of whether microglial purinergic receptors could be involved in pain and sexual dimorphism in RA.

Sex Differences in Pain Processing by the Brain

Other than DRGs or spinal cord changes, supraspinal structures involved with high-order functions, such as anxiety, depression, and cognition, are critical

component for pain processing.[63] There is a sex-related difference in brain structures involved in pain perception and modulation that can be explained, at least in part, by sex-hormones. Periaqueductal gray neurons, which project to the rostral ventral medulla and constituting the primary descending pathway of pain inhibition, express sex hormone receptors. AR and ERα immunoreactive neurons were widely distributed in the caudal periaqueductal gray neurons of male rats. Females had significantly fewer AR-positive neurons, although the quantity of ERα was comparable between the sexes.[153] A preclinical study showed that rostral anterior cingulate cortex, an important brain structure involved in pain affect, is also modulated by estrogen via ER.[154] Considering deep tissue pain in humans, brain imaging studies showed complex brain networks involved in sensory and affective aspects of pain. Under many chronic pain conditions, it was observed greater anterior cingulate cortex activation in females and insular cortex activation in males.[155] This sexual dimorphism of brain areas activation might contribute to different pain-related responses, which could require different treatment based on sex/gender differences. Although sex hormones have been suggested as key drivers of the sexual dimorphism observed in the expression of pain, an important sociocultural component must be also taking into account to explain the difference of pain experience in humans.

SUMMARY AND FUTURE DIRECTIONS

Epidemiologic and clinical findings demonstrate sex differences in several pain conditions, with women at higher risk of developing chronic pain. The central processing of pain information involving higher order neural functions can explain, at least in part, the sex-related differences in pain experienced by patients with RA. However, there is a dearth in the literature of studies directly addressing sex-associated differences and behavior in rodent models of inflammatory pain. As highlighted by Krock and colleagues,[104] nearly 50% of studies focused on pain-like behavior in arthritis were conducted only in male rodents. This observation reinforced that female and especially female/male comparisons in arthritis pain research are still needed. Although RA is an area of intense study, a single rodent model does not fully recapitulate disease. However, current models have been a useful tool to understand the pathophysiology and new targets to treat RA. Therefore, investigations with males and females are needed to advance our understanding of which components of the inflammatory processes that generate pain are subject to sex dimorphisms.

Therapies like nonsteroidal anti-inflammatory drugs have been used to treat pain in RA and in preclinical models of RA.[110,156] However, is important to note that studies suggest a neuropathic phenotype in RA-associated pain,[110,157] which would not be adequately treated by NSAIDs. Therefore, examining available treatments used to treat neuropathic pain might be valuable in addressing RA-associated pain. Strikingly, a sexual dimorphism has been seen when it comes to pain management in some animal models.[158] This finding highlights the necessity for understanding the phenotype of arthritis in both males and females to direct an effective treatment. It is noteworthy that, in parallel to biological factors, psychosocial and cultural factors contribute strongly to sexual dimorphism of pain perception in patients,[159–164] and consequently their response to therapy.

In conclusion, several animal models of RA have contributed our understanding of the pathogenesis of RA and therapeutic management. However, we still need to navigate through RA under a pain perspective, correlating key factors of RA that have not been tested in the pain context and considering both sexes.

CLINICS CARE POINTS

- Inflammatory joint pain exemplified in rheumatoid arthritis is regulated by different processes in males and females.
- Some, but not all, of the sex differences in pain processing are associated with sex hormones and their receptors.
- Sexual dimorphism in pain processing may also lead to sex differences in response to treatment and therapies should be evaluated for differences in efficacy in males and females.

DISCLOSURE

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